REMARKS:

Claims 1-3, 5, 6 and 8-19 are in the case and presented for consideration.

Claims 1-3, 5, 6 and 8-19 have been amended to improve their form.

Claim 7 has been canceled by this amendment and claims 4 and 20-25 were previously canceled, all subject to Applicants' right to claim their subject matter in one or more continuing applications.

At the outset, Applicants respectfully highlight that Claim 1 has already been amended to clarify that the claimed technical solution is directed to pharmaceutical composition containing (OC-6-43)-bis(acetato)-(1-adamantylamine)-amine-dichloroplatinic platinum complex of formula (II) as an active substance in a mixture with at least one pharmaceutically acceptable excipient wherein it is formed of a granulate with particles smaller than 0.5 mm in size prepared by wet granulation of a mixture of platinum complex of tetravalent platinum of formula (II) wetted by water, at least one neutral saccharide and at least one native and/or modified polysaccharide. See Amendment and Response dated April 27, 2009. Support for that amendment may be found at least at paragraphs [0020], [0021], [0028], [0039], [0040] and [0041] of the published application.

Applicants note that claim 1 has been further amended to clarify that the presently-claimed pharmaceutical is contained in a capsule or a sack or is pressed into a tablet form. Support for this amendment may be found at least at paragraph [0015] of the published application.

Rejections Under 35 U.S.C. §103(a)

Claims 1-11 have been rejected under 35 U.S.C. §103(a) as being unpatentable

over the publication by Mckeage et al. in *Cancer Chemot. Pharmcol* (1995)("Mckeage et al.") in view of U.S. Patent No. 6,503,943 Zak et al. ("Zak et al."), and U.S. Patent No. 6,221,393 to Collaueri et al. ("Collaueri et al."), and further in view of U.S. Patent No. 5,256,653 to Keppler et al. ("Keppler et al.") and U.S. Patent No. 5,900,252 to Calanchi et al. ("Calanchi et al.") as evidence by Swarbrick-Encyclopedia (1998). Official Action at p. 2.

The Office asserts that the claims are not directed to solving a technical solution but merely to a pharmaceutical composition containing platinum complex in a mixture of at least one pharmaceutical acceptable excipient formed of a granulate with particles smaller than 0.5 mm in size. Accordingly, the Office holds, in view of the combination of references, that it would have been *prima facie* obvious for one of ordinary skill in the art to have used the teachings of the prior art to obtain the claimed invention with a reasonable expectation of success. *Id.* at p. 4.

The Office disagrees with the view that Zak et al. does not contribute to anticipation of claim 1. It is asserted that Zak et al. was introduced to show that inclusion of excipients to form a platinum complex was known in the prior art before filing of the present application, and that Zak et al. ties in with the teachings of Mckeage et al. It is further asserted that Zak et al. was also employed for its teaching that the platinum complex is (OC-6-43) Bis (acetato)-(1-adamantylamine)-amine-dichloroplatinum. Thus, compounds of claims 1 and 4 were held to be obvious variations of formula (I), wherein the complex comprises a native saccharide, cyclodextrin, that may also be modified. *Id.* at p. 5.

The Office further asserts that the combined teachings of the references would have suggested to those of ordinary skill in the art to formulate a pharmaceutical composition containing a platinum complex. Using the specification to interpret the meaning of the

claims, the Office asserts that McKeage et al. teach the formulation in Example I of the specification wherein the composition for wet granulation comprises a platinum IV complex (i.e., JM 216), a modified starch (i.e., sodium starch glycolate); microcrystalline cellulose (i.e., a polysaccharide) and lactose. *Id.*

The Office acknowledges that Mckeage et al. lacks the teaching that the formulation is produced by wet granulation with particles smaller than 0.5 mm. It is asserted, however, that Kaplan et al. teach wet granulation of platinum IV complexes in a 0.5 mm range of particle size. *Id.*

The Office considers irrelevant with respect to the rejection under 35 U.S.C. §103 the argument that Collaueri et al. does not teach a platinum complex, because Collaueri et al. is used to show that granules entering into pharmaceutical compositions are advantageously prepared from a polysaccharide having particles less than 100 µM, which is less than 0.5 mm, and therefore is alternatively relevant to the formulation itself. *Id.* at pp. 5, 6.

The Office is unconvinced by the argument that different polysaccharides are used in Collaueri et al. because the skilled artisan, it is asserted, would have been motivated to employ polysaccharides other than xanthum gums in a wet granulation process with a neutral saccharide and a polysaccharide, as claimed in claim 2, because no specific type of polysaccharide is required in claims 2 and 6. The Office also notes that Collaueri et al. teaches that the composition is produced or processed by wet granulation. *Id.* at p. 6.

Thus, the Office holds that one of ordinary skill in the art would have substituted Mckeage et al.'s platinum IV complex with Zak et al.'s platinum complex to formulate a tablet by a wet granulation process with a reasonable expectation of success because wet granulation is used to improve flow, compressibility, bio-availability, and homogeneity of

low dose blends, electrostatic properties of powders, and stability of dosage forms. It was further held that one of ordinary skill in the art would have reasonably expected success in substituting Mckeage et al.'s compound JM 216 with Zak et al.'s compound ((OC-6-43) Bis(acetato)-(1-adamantylamine)-amine-dichloroplatinum) because both compounds are used for the same treatment conditions and substituting one for the other is within the purview of the skilled artisan. *Id.* at pp. 5, 6.

For the reasons that follow, Applicants respectfully traverse this rejection.

The Office remains reluctant to acknowledge the non-obviousness of the presently-claimed pharmaceutical composition, again asserting that the presently-claimed composition was obvious from the combination of Zak et al., Mckeage et al., Collaueri et al., and Kaplan et al.

The Office's argument derives its force from the view that the obviousness can be documented by means of a combination of prior art publications as in *KSR v. Teleflex, Inc,* No. 04-1350 (U.S. April 30, 2007). *KSR* obviousness is based on the statement "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." In other words, the known methods should hence comprise partial instructions or suggestions (familiar elements), respectively, the combination of which would direct the person skilled in the art to the same solution as claimed in the application.

In the following remarks, the Applicants will demonstrate, hopefully convincingly to the Office, that the combination of Zak et al./Mckeage et al./Collaueri et al./Kaplan et al.

does not comprise familiar elements, the combination of which would suggest the presently-claimed invention to a person skilled in the art. In addition, the Applicants will show that the above mentioned prior art publications teach, at some points therein, something other than what the Official Action characterizes them as teaching.

It follows from the above quoted statement from *KSR*, that the presently-claimed composition should be considered non-obvious unless the results reached by this composition are predictable from the combination of elements of the known methods according to Zak et al., Mckeage et al., Collaueri et al. and Kaplan et al. The results implied in the presently-claimed composition are the following: the presently-claimed composition comprising tetravalent platinum complex (very sensible to excipients) as active ingredient is prepared by wet granulation [as a result of which the undesirable properties of the tetravalent complex (insolubility in water, small bulk density, small tap density, and extremely high electrostatic charge) are eliminated] of the tetravalent platinum complex wetted by water together with specific excipients at the presence of which the tetravalent platinum complex is stable during and after the wet granulation (neutral saccharide and native and/or modified polysaccharide). The decision regarding whether the invention composition is obvious or non-obvious should be therefore dependent on whether the known methods according Zak et al., Mckeage et al., Collaueri et al. and Kaplan et al. comprise or do not comprise partial instructions or hints (familiar elements) that are mutually consistent (i.e. (a) concerning tetravalent platinum complexes, since the sensibility to the excipients is not the critical parameter for the bivalent platinum complexes, and (b) directed to the results reached by the invention composition) to such an extent that those partial instructions or suggestions could be logically combined to obtain the presently-claimed composition.

(1) The inclusion of Zak et al. among the publications - the combination of which should render the presently-claimed composition obvious - was inapposite, since Zak et al. is absolutely inconsistent with the results of the presently-claimed composition. Specifically, Zak et al. teaches a preparation of an inclusion complex of the tetravalent platinum complex by mixing a solution of the tetravalent platinum complex in an organic solvent with an aqueous solution of beta- or gamma-cyclodextrin and evaporating the solvent from the obtained solution (see line 60 of col. 2 to line 4 of col. 3 of Zak et al.). No wet agglomeration under water conditions is mentioned there. It is not therefore clear at all how the elements of this known method could be logically combined with the elements of the other publications to arrive at the presently-claimed composition when the method of Zak et al. is quite different, in the all process features, from the method for preparing the presently-claimed composition. The fact itself that Zak et al. provides a worse product in comparison with the presently-claimed composition gives rise to the strong, reasonable doubt that the person skilled in the art would have taken Zak et al. into consideration at all when working to a composition not having the known undesired properties of Zak et al.´s composition (this preparation is complex and costly and cyclodextrin capacity reduces significantly the content of tetravalent platinum complex). For these reasons the Applicants themselves refused to follow the Zak et al.´s way when aspiring to obtain the pharmaceutical composition of tetravalent platinum complex having good stability and sufficient content of the active ingredient (see paragraph [0004] of the published application).

Taking into account the foregoing, it is evident that Zak et al. cannot be used in the framework of *KSR* obviousness to support the obviousness of the presently-claimed composition, since it comprises no partial process feature at all which could be

hypothetically combined by a person skilled in the art with some other partial process features comprised in the other publications to arrive at presently-claimed composition prepared by the wet agglomeration. The affirmation justifying the submission of Zak et al., by which it would be shown that inclusion of excipients to form a platinum complex was known is, on its own, insufficient without the possibility of simultaneously proving that some familiar process elements of Zak et al. - hypothetically used in combination with the some familiar process elements of the other publication attending the *KSR* obviousness argumentation - lead to the presently-claimed composition. In fact, there is no such partial familiar process element in Zak et al..

(B) The publication Mckeage et al. teaches a stable pharmaceutical composition comprising tetravalent platinum complex JM216 as active ingredient and microcrystalline cellulose and lactose as excipients; that is to say, the composition substantially comprising the analogous active ingredient and the same principal excipients as comprised in the presently-claimed composition. As Mckeage et al. does not expressly mention any wet granulation, the Mckeage et al.´s composition should have been considered by the person skilled in the art either as a composition being prepared by simple dry blending of the concerned components or as a composition for which it is not certain whether it was prepared by the wet granulation of the concerned components. This ambivalent interpretability of the preparation of the Mckeage et al. composition would not have provided the person skilled in the art with the certitude of that he/she could have prepared a stable composition of the active ingredient of formula (II) as claimed in claim 1 of the present application (i.e. the presently-claimed composition) if he/she subjected the active ingredient of formula (II) to the wet granulation at the presence of the above-mentioned principal excipients used in Mckeage et al.´s publication in an effort to eliminate the above-

mentioned undesired properties. Nevertheless the fact that Mckeage et al. does not mention the wet granulation at all - despite that it was known that the wet granulation was able to eliminate the above-mentioned undesired properties of the substances (as the Office stated in the closing portion of page 5 of the preceding Office action) which properties should be supposed for the complex JM216 on the basis of analogy of the complex JM216 with the complex of formula (II) - the person skilled in the art should have arrived at the impression that the wet granulation was not recommended by Mckeage et al.

(C) As far as the newly submitted publication Kaplan et al. is concerned, the sense of the argument is unclear to the Applicant. The meaning of the Office Action´s sentence "As further evidenced by Kaplan et al., wet granulation of platinum IV complexes in a 0,5 mm range of particle size is (see col. 5, lines 37-41 and col. 8, lines 32-40)" is not clear, since the sentence evidently lacks a final portion. In addition, the Office interprets the content of the Kaplan et al. incorrectly when mentioning that the Kaplan et al. concerns the tetravalent platinum complexes ("platinum IV complexes"). Kaplan et al. deals, in fact, with bivalent platinum complex (microcrystaline form of cisplatin). This fact itself renders the content of Kaplan et al. inconsistent with the problem having to be solved when preparing the presently-claimed composition, since the sensibility to the excipients is not the critical parameter for the bivalent platinum complexes, and thus evidences in favor of that Kaplan et al. has not the capacity of being used in the framework of *KSR* obviousness against the obviousness of the presently-claimed composition. When interpreting the content of Kaplan et al., the Office reflects the following misinterpretations: (1) The Office compares the feature "0.5 mm range of particle size" as mentioned by Kaplan et al. (col. 5 lines 37-41) with the feature "smaller than 0.5 mm in size" as mentioned in claim 1 of the present

application and regards the similarity of the two features as also demonstrating the non-obviousness of the presently-claimed composition. But, the two features are, in fact, incomparable since the first of the two size ranges concerns the particle size of the microcrystalline cisplatin itself, i.e. non-granulated with the excipients, whereas the second of the two size ranges concerns the particle size the of the compound of formula (II) granulated together with the excipients (i.e. particle size of granulate). (2) The Office mentions the wet granulation in connection with Kaplan et al. But, the fact is, no such wet granulation of the concerned bivalent platinum complex (cisplatin) together with excipients is recommended by Kaplan et al. Kaplan et al. states that (A) "this invention relates to a stable, rapidly soluble, microcrystalline form of cisplatin, and to dry-mix formulation thereof" (col. 1, ll. 5-7); (B) "The aforementioned dry-mixes may be prepared by simply dry blending of the desired ingredients" (lines 32-34 of col. 8); (C) "With wet granulation procedures, it is preferred that that granulation be made of all ingredients except the cisplatin and that, after drying, the granulation be admixed with the desired amount of microcrystalline cisplatin." (Col. 8, ll. 36-39) The effort to protect the bivalent platinum complex against the relatively severe conditions of the wet granulation and avoid a decomposition of the platinum complex strongly ensues from Kaplan et al. When realizing that the tetravalent platinum complexes are notorious for being more sensible to any treating/working/handling than the bivalent platinum complexes are, it should be evident that the person skilled in the art - being aware of the content of Kaplan et al. and aspiring to prepare a stable pharmaceutical composition of the tetravalent platinum complex being free of the above-mentioned undesirable properties - should have arrived at the only possible conclusion, i.e. that Kaplan et al. teaches away from the wet granulation of the tetravalent platinum complex together with the excipients. On the other hand, it is clear that the composition

prepared by simply mixing the active ingredient with the excipients or by mixing the active ingredient with granulated excipients, as described in Kaplan et al. does not solve the problem of the mentioned undesirable properties of the tetravalent platinum complexes.

(D) Collaueri et al. teaches, analogously to Kaplan et al., a separate wet granulation of an excipient (xanthan gum), only, rather than the wet granulation of an active ingredient together with the excipients; the obtained pregranulated xantham gum is afterwards dry-blended with the active ingredient and optionally with the other used excipients. It is evident that Collaueri et al. does not solve, either, the problem of the substances showing the above-mentioned undesirable properties. This is because those substances remain at their original form, still exhibiting the above-mentioned undesired properties and influenced by no means by the wet granulation of the excipients with which the substances are later dry-blended and optionally further worked. Also in Collaueri et al., there is the evident endeavor to protect the pharmacologically active ingredient against the wet granulation conditions. Thus, Collaueri et al. also dissuades from the wet granulation of the tetravalent platinum complex implemented together with the excipients. The Office affirms that the only reason why it mentions Collaueri et al. is to show that granules entering into pharmaceutical compositions are advantageously prepared from a polysaccharide having particle less than 0.1 mm which is less than 0.5 mm." But this affirmation should be considered as having no probative force since the Office compares, in fact, two incomparable size ranges. The fact is the range "less than 0.1 mm" is related to particle size of a polysaccharide powder from which the pregranulated polysaccharide is prepared, whereas the range "smaller than 0.5 mm" relates to the particle size of the granulate consisting of the tetravalent platinum complex and the used excipient prepared by the wet granulation of the complex together with the excipients.

To summarize, when correctly interpreting the content of the above submitted prior art publications, the position of the person skilled in the art endeavoring - after obtaining a stable composition in frame of which the above-mentioned undesired properties of the tetravalent platinum complex of formula (II) are eliminated - would be, before the priority date of the present application, the following:

(a) The person skilled in the art would have been instructed by common professional knowledge that the above mentioned undesired properties of the tetravalent platinum complex of formula (II) could be eliminated by the wet granulation of the tetravalent platinum complex of formula (II), together with excipients.

(b) The person skilled in the art would have been instructed by Mckeage et al. (nevertheless, it should be noted that the instruction provided by Mckeage et al. is not quite unambiguous inasmuch as the Affidavit submitted by the Applicant´s reply to the preceding office action clearly shows that the stability of the compound of formula (II) at presence of an excipient need not be identical to that of the JM216 in presence of the same excipient as a result of which the analogy between the JM216 and compound of formula (II) need not be ever valid), on the basis of the analogy existing between the tetravelent platinum complex JM216 and tetravalent platinum complex of formula (II) in terms of their stability at presence of excipients, that suitable excipients for the wet granulation could optionally be lactose (sacharide) and cellulose (polysaccharide) as excipients, but under condition, only, that the person skilled in the art would have found in Kaplan et al. and/or Collaueri et al. an instruction of that an active ingredient analogous to the JM218 or compound of formula (II) was successfully (i.e. without causing an inadmissible decomposition of the active ingredient) subjected to the wet granulation together with excipients analogous to lactose and cellulose.

(c) The person skilled in the art would have been instructed by Kaplan et al. and Collaueri et al. that if the wet granulation is used, at all, then only the excipient(s) are separately (i.e. without active ingredient) wet granulated. This would have taught the person skilled in the art away from implementing the common wet granulation of the active ingredient together with the excipients. This practically, in turn, means that the condition of the point (b) necessary for denying the non-obviousness of the subject matter of the presently-claimed invention is not provided by Kaplan et al. and Collaueri et al.. So, the publications Zak et al., Mckeage et al., Kaplan et al. and Collaueri et al. do not comprise partial instructions which could be hypothetically and logically compiled together by the person skilled in the art to provide the presently-claimed composition. The fact that the Applicants reached the elimination of the undesired properties of the tetravalent platinum complex of formula (II) by wet granulating it together with the excipients - although he had been dissuaded, by Kaplan et al. and Collaueri et al., from such common wet granulation of the active ingredient together with the excipients - incontestably evidences that the subject-matter of the pending claims is non-obvious in view of Zak et al., Mckeage et al., Kaplan and Collaueri et al.

Inasmuch as the presently-claimed composition is defined in present claim 1 by the process of its formation, the above arguments are framed in terms of process features. Thus, this argumentation also supports the non-obviousness of the dependent process claims, namely in combination with the Applicant´s previous arguments concerning the other prior art publications (Keppler et al., Calanchi and Swarbrick-Encyclopedia). In any event, claims 2, 3, 5, 6 and 8-19 depend, either directly or indirectly from claim 1 and are therefore also believed to be patentable over the cited art.

In view of the foregoing, the Applicants respectfully submit that the presently-

claimed invention is not obvious in view of the combination of the cited references.

In addition, none of the above-mentioned references provide a teaching which would motivate one of ordinary skill to arrive at the presently-claimed invention.

Conclusion

Accordingly, Applicants believe that all the claims are now in condition for allowance and favorable action is respectfully requested. Should there be any issues that have not been addressed to the Examiner's satisfaction, Applicants invite the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, please charge such fees to Deposit Account No. 14-1431.

Respectfully submitted,

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